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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/606,618	06/26/2003	Ralph C. Judd	UM/SBC147BUSA	4915

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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	

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05/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/606,618	JUDD ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,30-36,39-42,50,52,55,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *57* is/are allowed.

6)☒ Claim(s) *25,30-36,39-42,50,52,55 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/03/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 01/09/09 in response to the non-final Office Action mailed 07/09/08.

Status of Claims

2) Claims 44-46 and 56 have been canceled via the amendment filed 01/09/09.

Claims 25 and 57 have been amended via the amendment filed 01/09/09.

Claims 25, 30-36, 39-42, 50, 52, 55, 57 and 58 are pending and are under examination.

Information Disclosure Statement

3) Acknowledgment is made of Applicants' Information Disclosure Statement filed 04/03/09. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

6) The rejection of claims 44-46 and 56 made in paragraph 41 of the Office Action mailed 12/15/06 and maintained in paragraph 16 of the Office Action mailed 08/14/07 and made/maintained in paragraph 9 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(b) as being anticipated by Manning *et al.* (*Microb. Pathogenesis*. 25: 11-22, July 1998, of record) (Manning *et al.*, 1998) in light of Richarme *et al.* (*Ann. Microbiol.* 133A: 199-204, 1982, of record), is moot in light of Applicants' cancellation of the claims.

7) The rejection of claims 44-46 made in paragraph 12 of the Office Action mailed 07/09/08

under 35 U.S.C § first paragraph, as containing new matter, is moot in light of Applicants' cancellation of the claims.

8) The rejection of claim 56 made in paragraph 13 of the Office Action mailed 07/09/08 under 35 U.S.C § first paragraph, as containing new matter, is moot in light of Applicants' cancellation of the claim.

9) The rejection of claims 44-46 and 56 made in paragraph 14 of the Office Action mailed 07/09/08 under 35 U.S.C § 112, first paragraph, as containing inadequate written description, is moot in light of Applicants' cancellation of the claims.

10) The rejection of claims 44-46 made in paragraph 16 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(e)(2) as being anticipated by Rubenfield *et al.* (US 6,551,795, filed 02/18/1998, of record) as evidenced by Harlow *et al.* (*In*: *Antibodies: A Laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, of record), is moot in light of Applicants' cancellation of the claims.

11) The rejection of claim 56 made in paragraph 17 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(b) as being anticipated by Dunn *et al.* (*Microbial Pathogenesis* 18: 81-96, 1995) as evidenced by Mignogna *et al.* (*J. Proteome Res.* 4: 1361-1370, 2005), is moot in light of Applicants' cancellation of the claim.

12) The rejection of claim 44-46 made in paragraph 18 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(b) as being anticipated by Chong *et al.* (WO 94/12641, already of record) ('641) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, of record), is moot in light of Applicants' cancellation of the claims.

13) The rejection of claim 56 made in paragraph 19 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(b) as being anticipated by West *et al.* (*Infect. Immun*. 47: 388-394, 1985) as evidenced by Manning *et al.* (*Microb. Pathogenesis*. 25: 11-22, July 1998, of record) (Manning *et al.*, 1998), is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

14) The rejection of claims 50, 55, 30 and 31 made in paragraph 10 of the Office Action mailed 07/09/08 under the judicially created doctrine of obviousness-type double patenting over claims 1 and 2 of the U.S. patent 6,610,306 (Applicants' IDS), is withdrawn in light of Applicants' submission of the terminal disclaimer filed 09/21/06.

15) The rejection of claim 25 and the dependent claims 39-42 made in paragraph 12 of the Office Action mailed 07/09/08 under 35 U.S.C § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the base claim. A new rejection is set forth below to address the claim(s) as amended.

16) The rejection of claims 25 and 39-42 made in paragraph 14 of the Office Action mailed 07/09/08 under 35 U.S.C § 112, first paragraph, as containing inadequate written description, is withdrawn in light of Applicants' amendment to claim 25.

17) The rejection of claims 25 and 39-42 made in paragraph 16 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(e)(2) as being anticipated by Rubenfield *et al.* (US 6,551,795, filed 02/18/1998, of record) as evidenced by Harlow *et al.* (*In*: *Antibodies: A Laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, of record), is withdrawn in light of Applicants' amendment to the base claim.

18) The rejection of claims 25 and 39-42 made in paragraph 18 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(b) as being anticipated by Chong *et al.* (WO 94/12641, of record) ('641) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, of record), is withdrawn in light of Applicants' amendment to the base claim.

Rejection(s) Maintained

19) The rejection of claims 25 and 39-42 made in paragraph 41 of the Office Action mailed 12/15/06 and maintained in paragraph 16 of the Office Action mailed 08/14/07 and paragraph 9 of the Office Action mailed 07/09/08 and the rejection of claims 55 and 58 made in paragraph 9 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(b) as being anticipated by Manning *et al.* (*Microb. Pathogenesis*. 25: 11-22, July 1998, of record) (Manning *et al.*, 1998) in light of

Richarme *et al*. (*Ann. Microbiol*. 133A: 199-204, 1982, of record), is maintained for the reasons set forth therein and herein. The rejection is still applicable to claims 55 and 58 due to the maintenance of the new matter rejection, and is also applicable to claim 25, as amended, and its dependent claims 39-42, because of the new matter rejection of the amended claim 25 and its dependent claims set forth below.

20) The rejection of claim 55 and the dependent claim 58 made in paragraph 13 of the Office Action mailed 07/09/08 under 35 U.S.C § first paragraph, as containing new matter, is maintained for the reasons set forth therein and those set forth in the paragraph immediately below.

21) The rejection of claims 55 and 58 made in paragraph 14 of the Office Action mailed 07/09/08 under 35 U.S.C § 112, first paragraph, as containing inadequate written description, is maintained for the reasons set forth therein and herein below.

Applicants have addressed both the new matter rejection and the lack of written description rejection together. Accordingly, the Office has rebutted Applicants' arguments together herein below.

Applicants contend that claims 55 and 58 are fully supported in the specification as written and as interpreted by one of skill in the art. Applicants state that claim 55 does not cover any stretch of 8 amino acids that can be found within SEQ ID NO: 4 and shared with other non-meningococcal or gonococcal microorganisms, as alleged, instead requires that (1) the polypeptide is isolated; (2) that the polypeptide comprise an epitope of *at least* 8AA of SEQ ID NO: 4; *and* (3) that the polypeptide induces antibodies that bind to SEQ ID NO: 4 and interfere with cell adherence in the assay described in Example 8. Applicants assert that one of skill in the art reading this disclosure clearly understands that the epitope must comply with all requirements of the claim and can be larger than 8 AA in length. Applicants submit that the paragraph spanning specification pages 20-21 provides an embodiment that the useful *fragments* of OMP86 are characterized by the ability to induce antibodies which interfere with binding of the pathogen to its cellular target, per the assay of Example 8, and may be as small as 5 up to fragments just less than the entire 700+ AA OMP85 protein. Applicants contend that OMP85 is a minor and less abundant OMP of *N. meningitidis* or *N. gonorrhoeae* and that Applicants were the first to realize the significance of the use of an immunogenic composition employing a polypeptide that

can induce sufficient antibodies that bind to OMP85, and prevent the pathogen from binding to the target cell. Applicants are the first to demonstrate in the assay of Example 8 that antibodies that bind to SEQ ID NO: 4 can be shown to block pathogen-target binding. Applicants state that: (a) they are the first to disclose the requirements of such an immunogenic composition; (b) The importance of Applicants' disclosure of this information as of the priority date of October 22, 1998 is demonstrated by the plethora of documents published after 1998 and focusing on uses of OMP85 in the meningitis vaccine field; (c) The specification provides written description at page 20, lines 25-29 through to page 21, line 4 that the full-length OMP85 or fragments of these sequences representing an epitope thereof, have the ability to induce antibodies to the cellular targets of *Neisseriae*, e.g., epithelial cells or mucosal cells, such as is exemplified in Example 8; and (d) All of this teaching, which is in the original priority specification, provides description sufficient for one of skill in the art to understand that the *N. meningitidis* and *N. gonorrhoeae* OMP85 proteins contain an epitope sequence that is recognized by the antisera developed to the exemplified *N. gonorrhoeae* OMP85. Applicants further state that: (e) Example 8 provides written description of the use of a sequence containing an epitope found within an OMP85 amino acid sequence; (f) The OMP85 sequence SEQ ID NO: 2 has at least 95% sequence similarity to SEQ ID NO: 4; (g) Example 8 is stated as disclosing the use of antisera developed to a fusion protein of *the first 178 AA of SEQ ID NO: 2*; the 178AA sequence differing between the two species by 3 amino acids, as shown in Fig. 5; and (h) The specification at Example 7 and Figure 6 provides written description that the same antisera bound to OMP85 proteins of various *N. meningitidis* and *N. gonorrhoeae* strains in the Western blot. Applicants assert that this description conveys to one of skill in the art that antisera to amino acid 1-178 of SEQ ID NO: 2 binds to the OMP85 sequence of SEQ ID NO: 4. This is evidence that both the *N. gonorrhoeae* and *N. meningitidis* OMP85 proteins contain at least one common epitope sequence capable of inducing similarly binding antisera. Applicants cite case law and state that this would be clearly understood by one of skill in the art considering the degree of identity of the SEQ ID NO: 2 and 4 sequences, as well as the virtual identity of the two sequences in the span of amino acids 1-178. Applicants state that it is not necessary for written description of this invention to define precisely the epitope of OMP85 itself, but it is sufficient for written description of this invention that Applicants have described the OMP85 protein or polypeptide that contains an epitope to

which the antisera binds and that is capable of inducing the antisera for use in an immunogenic composition. Applicants assert that one of skill in the art is aware that the identification of the precise epitope is not necessary in order to identify a protein or polypeptide useful to induce antisera. Applicants state that the description and teaching at page 20, lines 25-29 coupled with the description and teaching of Example 8 provides the essential written description to convey to the person of skill in the art that antisera to an OMP85 protein with the extremely high degree of similarity to SEQ ID NO: 4 also prevents binding between a *Neisseria* species, e.g., the *N. gonorrhoeae* species exemplified, and the known cellular target, i.e., an epithelial cell. Applicants assert that the specification provides written description for the selection and use of the *Neisseria gonorrhoeae* and *Neisseria meningitidis* OMP85 proteins and fragments thereof as useful immunogens, the strong homology of the sequences between the *Neisseria gonorrhoeae* and *Neisseria meningitidis* species (described functionally and by analysis of the two exemplified amino acid sequences SEQ ID NOs: 2 and 4) and the ability of these proteins or fragments thereof to induce antisera in a mammal, e.g., a laboratory rabbit model, that can interfere with the ability of the *Neisseria* pathogen to attach to its cellular target. As the prior art at the time of filing of the priority document, was aware that invasion of epithelial cells was critical to infection by *Neisseria* pathogenic species, this specification identified the value of these OMP85 proteins, as opposed to the more abundant major outer membrane proteins (e.g., PorA/PorB) known in the art for these pathogens. Applicants state that further support can be found by comparison of the OMP85 sequence of *N. gonorrhoeae* FA1090 (GenBank No. AAW90419) shown in the specification's description and Figs. 3 and 6, with *N. meningitidis* HH OMP85. These sequences are also 95% identical.

Applicants' arguments have been carefully considered, but are not persuasive.

Claim 55 requires that (a) the polypeptide is isolated; (b) that the polypeptide comprise an epitope of ***at least* 8** amino acids of SEQ ID NO: 4; *and* (3) that the polypeptide induce antibodies that bind to SEQ ID NO: 4 and interfere with the adherence of *Neisseria gonorrhoaeae* as measured by the gonococcal cell adherence assay. Claim 55 does not recite a fragment comprising the first 178 amino acids of SEQ ID NO: 2, or a sizeless epitope. Instead, the minimum required size of the epitope recited in claim 55 is eight consecutive amino acids of SEQ ID NO: 4. The epitope recited therein also encompasses for example nine amino acid-long

eptipes, ten amino acid-long epitopes, eleven amino acid-long epitopes, twelve amino acid-long epitopes, thirteen amino acid-long epitopes of SEQ ID NO: 4 etc., each having the recited functions. Claim 55 does not cover any stretch of generic, non-functional 8 amino acids within SEQ ID NO: 4, but those which are specific to gonococci alone, specific to gonococci and meningococci, and those shared by gonococci, meningococci and also by non-gonococci and non-meningococci, and having the ability to induce antibodies that interfere with the adherence specifically of *Neisseria gonorrhoaeae* as measured by the gonococcal cell adherence assay. A mere statement that the specification provides an embodiment that the useful *fragments* of OMP86 are characterized by the ability to induce antibodies which interfere with binding of an unspecified pathogen to its cellular target, per the assay of Example 8, and may be as small as 5 up to fragments just less than the entire 700+ AA OMP85 protein, is not sufficient to meet the written description provision of 35 U.S.C § 112, first paragraph. Furthermore, the descriptive support and the evidence of possession have to come from Applicants' specification as originally filed, and not from the documents published after 1998. Given the art-recognized non-specificity of multiple eight amino acid-long epitopes from within SEQ ID NO: 4 (see sequence alignments documented at paragraph 14 of the Office Action mailed 07/09/08) , there is absolutely no predictability that any unidentified at least eight amino acid-long epitopes of SEQ ID NO: 4, or any epitopes comprising less than the first 178 amino acid residues of SEQ ID NO: 2, would have the meningococcus-specificity and/or gonococcus-specificity, and the ability to induce antibodies in a mammal that bind to SEQ ID NO: 4 *and* that interfere with the adherence of *Neisseria gonorrhoeae* as measured by the gonococcal cell adherence assay. It should be noted that neither Example 7 nor Example 8 identifies one single eight amino acid-long epitope species, ten amino acid-long, twelve amino acid-long, fifteen amino acid-long etc. epitope species within either SEQ ID NO: 4 or within the first 178 amino acids of SEQ ID NO: 4 that is meningococcus-specific and/or gonococcus-specific, *and* that induces antibodies in a mammal that bind to SEQ ID NO: 4 *and* that interfere with the adherence of *Neisseria gonorrhoeae* as measured by the gonococcal cell adherence assay. The paragraph bridging pages 20 and 21 of the instant specification states as follows [Emphasis added]:

> Further encompassed by this invention are additional fragments of the Omp85 polypeptides and peptides identified herein. Such fragments are desirably characterized by having a biological activity similar to that displayed by the complete protein, including, e.g., the ability to induce antibodies which can

> interfere with the binding of the pathogen to its cellular targets (see Example 8). These fragments may be designed or obtained in any desired length, including as small as about 5-8 amino acids in length up to fragments encompassing just short of the entire protein. Such fragments **may** represent consecutive amino acids in the protein sequence or they **may** represent conformational sites of the protein. Such a fragment **may** represent an epitope or conformational epitope of the protein.

Contrary to the Applicants' assertion, the specification at page 20, lines 25-29 through to page 21, line 4 neither provides descriptive support for the at least *eight* amino acid-long epitope of SEQ ID NO: 4 as recited, nor reduces or traces the gonococcal cell adherence-inhibiting conformational and/or non-conformational epitope to an *eight* amino acid-long epitope species, ten amino acid-long, twelve amino acid-long, fifteen amino acid-long etc. epitope species of SEQ ID NO: 4 or of the first 178 amino acid-long fragment of SEQ ID NO: 4. The rejection of record has documented the art-known fact that not all eight amino acid-long epitopes from within SEQ ID NO: 4 are meningococcus-specific and/or gonococcus-specific, let alone induce antibodies that interfere with the adherence of *Neisseria gonorrhoeae* as measured by the gonococcal cell adherence assay. Except for one fragment species consisting of the first 178 amino acids of SEQ ID NO: 2 that elicits antibodies which bind to SEQ ID NO: 4 and interfere with the adherence of *Neisseria gonorrhoeae* as measured by the gonococcal cell adherence assay, Applicants did not have possession of a representative number of epitope species of SEQ ID NO: 4 that are eight amino acid-long epitope species, ten amino acid-long, twelve amino acid-long, fifteen amino acid-long etc. epitope species having the *requisite* functions. A sufficient number of representative species must be included 'to demonstrate that the patentee possesses the full scope of the [claimed] invention', which is lacking in the instant case. *Lizardtech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1345, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005). Applicants should note that written description requires more than a mere statement that something is a part of the invention and a reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

As set forth previously, the *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

However, in the instant case, the precise structure of a representative number of epitope species of SEQ ID NO: 4 that are eight amino acid-long, ten amino acid-long, twelve amino acid-long, fifteen amino acid-long etc. has not been correlated with the *requisite* functions, i.e., the ability to induce antibodies that bind to SEQ ID NO: 4, the meningococcus-specificity and gonococcus-specificity, and the ability to interfere with the adherence of *Neisseria gonorrhoeae* as measured by the gonococcal cell adherence assay. As set forth in the rejection of record, this is critically important due to the art-reported sharing of several fragments of SEQ ID NO: 4 not only with the D-15-Ag of *H. influenzae* and Oma87 protein of *Pasteurella multocida* as disclosed by Applicants' own specification (see lines 16-19 of page 10 and Figure 5 of the instant specification), but also by the sequences of at least *Arabidopsis thaliana, Pyrococcus abyssi*, the *hyper-thermophilic archaebacterium Pyrococcus horikoshii OT3, Vibrio cholerae,* and *Bacillus subtilis*. The rejection of record also established via at least one example that the eight amino acid-long sequence, IDEGKSAK, falling within Applicants' 178 amino acid-long fragment of SEQ ID NO: 2 or 4 described in Figure 5 of Applicants' specification is not meningococcus-specific and/or gonococcus-specific, but is shared by *Bacillus subtilis.* The binding of the antisera raised to a fusion protein of the first 178 amino acid residues of SEQ ID NO: 2 is not limited to the OMP85 proteins of specific *N. meningitidis* and *N. gonorrhoeae* strains as shown in Figure 6, but the binding of that antisera also occurs with multiple, generally non-pathogenic strains of *Neisseria* such as *N. pharyngis, N. cinerea, N. lactamica, N. mucosa, N. flavescens* and *N. denitrificans* as depicted in Figure 7A. Clearly, Applicants did not have possession of a representative number of 8, 9, 10, 11, 12, 13, 14, 15 etc, amino acid-long epitope species of SEQ ID NO: 4, from either within or outside of the first 178 amino acids of SEQ ID NO: 4, which epitope species are meningococcus-specific and gonococcus-specific, immunogenic and that induce SEQ ID NO: 4-specific antibodies that interfere with the adherence of *Neisseria gonorrhoeae* as measured by the gonococcal cell adherence assay. The precise structure of such specific epitopes has not been correlated with the recited requisite functions. Without a concrete structure-function correlation, the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. Appl. & Int. 2007) citing *Eli Lilly*, 119 F.3d at 1568, 43 USPQ at 1406 ('definition by function ….. does not suffice to define the genus because it is only an indication

of what the gene does, rather than what it is'). Clearly, claim 55 and the dependent claim 58 do not meet the provision of 35 U.S.C § 112, first paragraph. The rejection stands.

22) The rejection of claim 55 made in paragraph 16 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(e)(2) as being anticipated by Rubenfield *et al.* (US 6,551,795, filed 02/18/1998, of record) as evidenced by Harlow *et al.* (*In*: *Antibodies: A Laboratory Manual.* Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, of record), is maintained for the reasons set forth therein and herein below.

Applicants contend that claim 55 does not cover any stretch of 8 amino acids that can be found within SEQ ID NO: 4, but requires that the polypeptide is isolated; that the polypeptide comprise an epitope of at least 8 AA of SEQ ID NO: 4; and that the polypeptide induce antibodies bind to SEQ ID NO: 4 and interfere with cell adherence in the assay described in Example 8. Applicants state that the epitope must comply with all requirements and can be larger than 8 AA in length. Applicants submit that the paragraph spanning specification pages 20-21 provides an embodiment that the useful fragments of OMP85 are characterized by the ability to induce antibodies which interfere with binding of the pathogen to its cellular target, per the assay of Example 8, and may be as small as 5 up to fragments just less than the about 709 AA OMP85 protein. Applicants argue that other than the minimal length, Rubenfield's 8-mer does not meet any of Applicants' requirements and that it is not isolated. Applicants state that there is no evidence or teaching that Rubenfield's 8-mer, directed to a completely different pathogen, induces antibodies that interfere with binding of a neisserial pathogen to its cellular target.

Applicants' arguments have been carefully considered, but are not persuasive.

The structural requirement of the epitope recited in claim 55 is that it is comprised within SEQ ID NO: 4 and that it is at least eight consecutive amino acids in length anywhere within SEQ ID NO: 4. As set forth in paragraph 16 of the Office Action mailed 07/09/08, Rubenfield *et al.* disclosed an isolated or a substantially pure polypeptide having the amino acid sequence of SEQ ID NO: 24628 comprising the eight consecutive amino acids, VRVETADG, which eight consecutive amino acids are *identical* to the eight amino acid-long fragment, VRVETADG, located at amino acid positions 74 through 81 of the instantly recited SEQ ID NO: 4, i.e., an eight amino acid-long epitope located within the first 178 amino acid-long N-terminal sequence of SEQ ID NO: 2 that is used in Example 8 of the instant specification. A therapeutic or prophylactic

vaccine comprising the polypeptide and a pharmaceutically acceptable carrier as well as a diagnostic composition, a diagnostic reagent capable of providing a detectable signal comprising the polypeptide modified with a label, such as a radioisotope or a fluorescent label, was taught by Rubenfield *et al*. A diagnostic kit comprising the polypeptide being present on immobilization means such as particles, supports (inclusive of latex), wells, dipsticks, and the nitrocellulose papers containing the polypeptide, was also disclosed. The polypeptide existed as a recombinant fusion protein fused to a polyhistidine sequence, i.e., fused to a second heterologous protein or polypeptide. The polypeptide was co-administered with an adjuvant. See Sequence Listing; third full paragraph in column 5; first three paragraphs in column 6; lines 18-29 in column 11; and 'Vaccine Formulations for P. aeruginosa …. Polypeptides' in columns 37-40; section 'Kits Containing … Polypeptides of the Invention'; and lines 1-5 of column 42. See also the sequence alignment below:

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US-09-252-991A-24628
Sequence 24628, Application US/09252991A
Patent No. 6551795
GENERAL INFORMATION:
APPLICANT:  Marc J. Rubenfield et al.
TITLE OF INVENTION: NUCLEIC ACID AND AMINO ACID SEQUENCES RELATING TO PSEUDOMONAS
TITLE OF INVENTION:  AERUGINOSA FOR DIAGNOSTICS AND THERAPEUTICS
FILE REFERENCE:  107196.136
CURRENT APPLICATION NUMBER: US/09/252,991A
CURRENT FILING DATE:  1999-02-18
PRIOR APPLICATION NUMBER:  US 60/074,788
PRIOR FILING DATE:  1998-02-18
PRIOR APPLICATION NUMBER:  US 60/094,190
PRIOR FILING DATE:  1998-07-27
NUMBER OF SEQ ID NOS:  33142
SEQ ID NO 24628
LENGTH: 648
TYPE: PRT
ORGANISM: Pseudomonas aeruginosa
US-09-252-991A-24628
Query Match              1.0%;  Score 8;  DB 4;  Length 648;
Best Local Similarity   100.0%;  Pred. No. 35;
Matches  8;  Conservative  0;  Mismatches  0;  Indels  0;  Gaps 0

Qy         74 VRVETADG 81
              ||||||||
Db         94 VRVETADG 101
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Since the isolated prior art polypeptide is not fully purified, it is expected to inherently contain at least a residual second *P. aeruginosa* protein or polypeptide contaminant, i.e., second polypeptide or protein antigen from a pathogenic species heterologous to *Neisseria meningitidis* or *Neisseria gonorrhoeae*. That the prior art polypeptide containing therein the 8 amino acid-long epitope,

VRVETADG, induces antibodies which bind to the instant polypeptide of SEQ ID NO: 4 or any other neisserial protein including the gonococcal protein that contains the epitope as recited in the instant claim 55 is inherent from the teachings of the prior art, since such a polypeptide is well known in the art to be long enough to elicit an antibody response in a mammal. The art recognizes that the smallest peptides that elicit antibodies which bind to the original full-length protein are 6 amino acids in length. See first sentence under 'Size of the Peptide' on page 76 of Harlow *et al*. Furthermore, although Rubenfield *et al*. are silent about the ability of their eight consecutive amino acid-containing polypeptide to induce antibodies in a mammal that interfere with adherence of *Neisseria gonorrhoeae* as measured by the gonococcal cell adherence assay as recited in the instant claim 55, the prior art polypeptide epitope is viewed as the same as the Applicants' polypeptide epitope because of the *identical* structural composition. In spite of the fact that the prior art fails to teach all of the disclosed functional characteristics of the Applicants' polypeptide epitope, there is total structural epitopic identity to conclude that the prior art eight consecutive amino acid-containing epitope, VRVETADG, falling well within the first 178 amino acids of the instantly recited SEQ ID NO: 4, is one and the same as the Applicants' eight consecutive amino acid-containing epitope. Since the prior art eight consecutive amino acid-long epitope is structurally the same as the eight consecutive amino acid-containing epitope recited in the instant claims and is an epitope contained within the first 178 amino acids of SEQ ID NO: 2 that is used to induce antibodies in Example 8 of the instant specification, it is expected to necessarily have the same intrinsic binding and adherence-interfering properties as that of the Applicants' epitope or polypeptide. Applicants have not identified one or more specific eight amino acid-long epitopes within the SEQ ID NO: 4 that induce antibodies in a mammal which interfere with the adherence of *Neisseria gonorrhoeae* as measured by the gonococcal cell adherence assay, and therefore, the prior art epitope VRVETADG is certainly not excluded from the scope of the claim. 'Products of identical chemical composition can not have mutually exclusive properties.' A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant recites and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). To the extent the embodiment in the claimed invention achieves induction of antibodies that bind to SEQ ID NO: 4 and interfere with the adherence of *Neisseria gonorrhoeae* as measured by the

gonococcal cell adherence assay, so does the VRVETADG epitope-containing isolated or substantially pure polypeptide of Rubenfield *et al.* The rejection stands.

23) The rejection of claims 50, 52, 55 and 30-36 made in paragraph 17 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(b) as being anticipated by Dunn *et al.* (*Microbial Pathogenesis* 18: 81-96, 1995, of record) as evidenced by Mignogna *et al.* (*J. Proteome Res.* 4: 1361-1370, 2005, of record), is maintained for the reasons set forth therein and those set forth in the paragraph immediately below.

24) The rejection of claims 50, 52 and 55 made in paragraph 19 of the Office Action mailed 07/09/08 under 35 U.S.C § 102(b) as being anticipated by West *et al.* (*Infect. Immun.* 47: 388-394, 1985, of record) as evidenced by Manning *et al.* (*Microb. Pathogenesis.* 25: 11-22, July 1998, of record) (Manning *et al.*, 1998), is maintained for the reasons set forth therein and herein below.

Applicants have addressed both the prior art rejections of Dunn *et al.* and West *et al.* together. Accordingly, the Office has rebutted Applicants' arguments together herein below.

Applicants contend that Dunn 1995 discloses a typical preparation of *N. meningitidis* 'MS58' outer membrane vesicles, i.e., by suspending bacterial colonies in PBSB, followed by serial vortexing, centrifugations and filtering. Applicants state that Dunn tested the resulting OMV for toxicity on human umbilical vein endothelial cells; no information on immunogenicity was provided by this document. Applicants argue that Mignogna 2005 is a proteomic study that identified 210 protein species from this bacterium, which identifies OMP85 as an 'MS58' protein. Applicants state that they do not challenge the fact that OMP85 is a minor outer membrane protein of this bacterium. Mignogna is alleged as stating that the major OMPs of 'MS58' preparation were P.IA and P. IB.

Applicants assert that similarly to the disclosure of Dunn, the methods and materials paragraphs of West 1985 merely recite the preparation of crude membrane preparation from the cultured *N. gonorrhoeae* FA 19 bacteria grown under wild-type or iron-repressed culture conditions. Applicants state that (a) Figure 1 shows the response of FAl9 to iron limitation after dilution of the culture with Desferal, an iron chelator; (b) The arrows on the gel point to positions on the gel between the 67 and 97 kDa markers induced due to iron limitation, an unnatural culture condition. Clearly the gel indicates considerably less of the induced protein in

comparison to the abundant proteins appearing on other areas of the gel in both the control and iron-limited cultures. Fig. 2, in addition to noting that the major FA19 OMP protein is between markers 30 and 43 kDA, shows essentially similar information. Further note that in col. 1 of page 391, West reports that an "additional" iron-repressible protein of 88K was present when hemoglobin was the iron source in the culture. Applicants assert that nothing else is stated about this protein in West or in Manning to indicate whether it is present in the crude preparation in sufficient amounts to induce anti-OMP85 antibody in a mammal. Neither Dunn nor West can serve as § 102 prior art because neither Dunn's OMV nor West's crude preparation are identical to the immunogenic composition of Applicants. Applicants state that Mignogna does not teach that Dunn's composition is the same as Applicants; that Manning does not teach that West's composition is the same as Applicants; and that neither Dunn with Mignogna nor West with Manning teach a composition with sufficient OMP85 to induce antibodies in a mammal that bind to said amino acid sequence of SEQ ID NO. 4 and that interfere with adherence of *Neisseria gonorrhoeae* as measured by the gonococcal cell adherence assay, as required by Applicants' claims. Applicants argue that OMP85 is not one of the major OMPs produced in OMVs of *N. meningitidis* and that conventionally prepared OMVs (circa the 1998 priority date of this application) naturally contain much larger amounts of the major OMPs than the minor OMPs. Applicants allege that these compositions containing abundant amounts of the major OMPs, such as PorA, would upon administration to a mammal, induce measurable antigenic responses to the major OMPs and none or undetectable immune responses to the minor proteins such as OMP85. Applicants acknowledge that prior art OMVs or blebs may have contained some minor amounts of the conserved OMP85 polypeptide, but speculate that any antibody that may have developed to the minor OMPs in such compositions were swamped by antibody response to the naturally occurring, predominant OMPs. Applicants further state that overproduction of antisera to the predominant OMP in OMVs is one of the reasons for the failure of the prior art before 1998 to recognize the importance of OMP85 in immunogenic compositions. Applicants further speculate that the circa 1998 OMVs or crude preparations produced by centrifugation and/or detergent treatment, such as that of Dunn or West, did not contain sufficient OMP85 to elicit detectable antibodies to the minor OMP. Applicants attached the post-filing reference of Weynants *et al.* 2007 *Infect. Immun.*, 75(11): 5434-5442 as Exhibit A and state that Weynants *et al.* demonstrate

that animals immunized with OMVs from strains that did not overproduce OMP85 (compared to a wild type control) produced no detectable antibodies directed against OMP85. Applicants point to Figure 2B of Weynants *et al.* and state that only when Weynants provided a recombinant bacterial strain that overproduced OMP85 did the animal's antisera produce detectable anti-OMP85 antibodies. This data is alleged as demonstrating that a conventional, non-overproducing OMV, such as provided by Dunn or West, would not have contained sufficient OMP85 to elicit detectable antibodies to SEQ ID NO: 4 and thus interfere with cellular adhesion. Applicants state that their immunogenic composition is required to have sufficient OMP85 to induce an antibody response measurable on the cellular adhesion assay of Example 8.

With regard to the reference of Manning *et al.* (1998), Applicants state that the pending specification is a continuation of the prior application filed October 22, 1998 and has the same specification with minor formal and grammatical corrections, and that Manning, a publication of the inventors' published less than one year prior to the priority date, is not § 102(b) prior art for any claim entitled to claim priority to the original application. Applicants further state that the previously filed *In re Katz* declaration removes Manning from citation as § 102(a) prior art.

Applicants' arguments have been carefully considered, but are not persuasive. First, the open claim language 'comprising' in the claim does not exclude the presence of major OMPs or any other elements from the scope of the claimed composition. Second, the claimed composition is required to comprise an isolated polypeptide as recited, but is not required to contain 'sufficient' OMP85, whatever that amount may be. The recited polypeptide is not required to be produced under natural culture conditions, but encompasses one produced under any condition, and is not required to be induced in considerably high amounts compared to other abundant proteins appearing on a gel. Any additional iron-repressible protein of 88K is not excluded from the scope of the claimed composition due the use of the open claim language 'comprising'. Contrary to Applicants' speculation, nothing in Dunn *et al.* or West *et al.* indicates that the Omp85 protein intrinsically contained in their composition is not present in sufficient amounts to induce anti-OMP85 antibody in a mammal. With regard to the Office's rejection over Dunn *et al.*, Applicants' arguments on 'MS58' are irrelevant, since neither the art rejection of record nor the teachings of Dunn *et al.* pertain to 'MS58'. As set forth therein both Dunn's OMV composition and West's OMP composition are expected to intrinsically comprise therein an

Omp85 polypeptide isolated or separated from the cellular mass of MC58 strain of *N. meningitidis* and FA19 strain of *Neisseria gonorrhoeae* respectively, the *same two strains* identified in Exhibit C filed 02/06/06 along with the Judd declarations as the producers of Omp85 polypeptide that is at least 95% identical to the instantly recited SEQ ID NO: 4. Therefore, each outer membrane composition would be expected by those of skill in the art to be intrinsically immunogenic, wherein the Omp85 polypeptide present therein along with the homologous LPS adjuvant, is expected to induce antibodies in a mammal that would necessarily have the same functions as that of Applicants' composition. Contrary to Applicants' assertion, isolated neisserial outer membrane preparations including isolated outer membrane vesicles comprising a mixture of proteins such as PorA, PorB and Omp85 have been shown in the art to elicit detectable antibody response to the Omp85 component contained therein. For instance, Wedege *et al.* (*Clin. Vaccine Immunol.* 14: 830-838, July 2007) demonstrate that the Norwegian MenBvac OMV vaccine and the MeNZB OMV vaccine comprising PorA, PorB, Omp85, FetA, FbpA, RmpM and LPS immunogen components therein, elicited significant levels of IgG antibodies to the Omp85 polypeptide component. See paragraph bridging pages 830 and 831 as well as pages 833 and 834 and the first full paragraph on page 836. Likewise, the post-filing reference of Weynants *et al.* (*Infect. Immun.* 75: 5434-5442, November 2007) attached to Applicants' amendment/response filed 01/09/2009 expressly teaches that Rosenqvist's (1995) wild type OMV vaccine did elicit detectable bactericidal antibodies against an 80 kDa protein after immunization with the wild-type vaccine (see left column on page 5435), thus indicating that a detectable anti-80 kDa protein response is induced by wild type OMV vaccines that contain a mixture of Por proteins and an 80 kDa protein. Lanes 1 and 7 of Figure 2A of Weynants *et al.* clearly show that the wild type OMVs from H44/76 strain of *N. meningitidis* contained sufficient amounts of Omp85 polypeptide. With regard to Weynants' alleged teaching that animals immunized with OMVs from strains that did not overproduce OMP85 produced no detectable antibodies directed against OMP85, it should be noted that the only conclusion that can be drawn is that 5 micrograms of one OMV preparation of H44/76 strain used by Weynants *et al.* to immunize mice showed an anti-Omp85 antibody titer of <50 when measured by one assay, ELISA. Instant claims do not have a limit on the amount of OMV contained in the claimed composition, the number of immunizations that can be used to elicit antibodies, and the

use of assays much more sensitive than ELISA to detect Omp85 antibodies. Contrary to Weynants *et al.*, and consistent with Applicants' acknowledgment that prior art OMVs or blebs may have contained some minor amounts of the conserved OMP85 polypeptide, Norheim *et al.* (*Vaccine* 23: 3762-3774, 2005) demonstrate that meningococcal OMV vaccines from different strains comprise not only several major outer membrane proteins, but also several other proteins including Omp85 in small amounts (see abstract) and in amounts readily detectable by 12% SDS-PAGE gel (see Figure 1), and upon immunization of mammals induce sufficient anti-Omp85 antibodies that identify the Omp85 polypeptide by immunoblot assay. See Figure 4. Clearly, the teachings of Dunn *et al.* or West *et al.* anticipate the instant claims. The alleged failure of Dunn *et al.* or West *et al.* to expressly mention the immunogenicity of their outer membrane composition as a goal is irrelevant. Immunogenicity is an inherent property inseparable from the prior art outer membrane composition. To the extent the composition embodiment in the claimed invention achieves immunogenicity or induction of antibodies as recited, so does the composition of Dunn *et al.* or West *et al.* Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results, i.e., immunogenicity in the instant case. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983). With regard to Applicants' contention that the previously filed *In re Katz* declaration removes Manning from citation as § 102(a) prior art, Applicants should note that Manning *et al.* (1998) was used as an as evidenced by type reference (and not as a prior art reference under 35 U.S.C. § 102(a)), to show that every element of the claimed subject matter is disclosed by West *et al.* with the unrecited limitation(s) being inherent in view of what is known in the art as taught in Manning *et al.* (1998). See *In re Samour* 197 USPQ 1 (CCPA 1978). Manning *et al.* (1998) was cited to show that the missing inherent matter is necessarily present in the thing described in the prior art reference of West *et al.* 'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. MPEP 2124. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v.*

Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). Also note that the critical date of extrinsic evidence showing a universal fact need not antedate the filing date. See MPEP 2124. Therefore, the *In re Katz* declaration does not remove Manning *et al.* (1998). The art rejections stand.

New Rejection(s) Necessitated by Applicants' Amendment
Rejection(s) under 35 U.S.C § 112, First Paragraph

25) The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

26) Claim 25 and the dependent claims 39-42 are rejected under 35 U.S.C § first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 25, as amended, deletes the limitation: 'or having an amino acid sequence which comprises an epitope of said SEQ ID NO: 4' and includes the new limitations: 'for *Neisseria meningitidis* and *Neisseria gonorrhoeae*'. As amended, claim 25 is now drawn to a 'diagnostic composition for *Neisseria meningitidis* and *Neisseria gonorrhoeae*' comprising an isolated polypeptide having an amino acid sequence of 95% or greater sequence identity with the amino acid sequence of SEQ ID NO: 4, said polypeptide associated with a suitable detectable label. Applicants do not point to specific parts of the specification that support this amendment, but state that the amendment finds support in the original specification. However, as known in the art, a polypeptide composition is or can be 'diagnostic' of a particular disease, infection, medical condition, or clinical condition, but not 'diagnostic' for a pathogen such as a bacterial pathogen. A review of the specification indicates that there is no descriptive support for a 'diagnostic'

composition, i.e., a composition that is 'diagnostic for *Neisseria meningitidis* and *Neisseria gonorrhoeae*' that comprises an amino acid sequence of 95% or greater sequence identity with the amino acid sequence of SEQ ID NO: 4, said polypeptide is associated with a suitable detectable label. Furthermore, Figures 6 and 7A of the instant specification appear to indicate that antibodies elicited by the first 178 amino acid of SEQ ID NO: 2 also recognizes the Omp85 polypeptides in various other *Neisseriae* other than *Neisseria meningitidis* and *Neisseria gonorrhoeae* including normally non-pathogenic *Neisseriae* such as *N. pharyngis, N. cinerea, N. lactamica, N. mucosa, N. flavescens* and *N. denitrificans,* indicating that a composition comprising an amino acid sequence of 95% or greater sequence identity with the amino acid sequence of SEQ ID NO: 4, wherein the polypeptide is associated with a suitable detectable label is not specifically 'diagnostic' for *Neisseria meningitidis* and *Neisseria gonorrhoeae,* but may also identify non-pathogenic *Neisseriae* such as *N. pharyngis, N. cinerea, N. lactamica, N. mucosa, N. flavescens* and *N. denitrificans.* Therefore, the above-identified limitation in the amended claim 25 is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P § 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the new limitation(s), or alternatively remove the new matter from the claim(s). Applicants should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

27) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

28) Claims 25 and 39-46 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 25, as amended, is indefinite, confusing and/or incorrect in the limitation: diagnostic composition 'for *Neisseria meningitidis* and *Neisseria gonorrhoeae*', because it is

unclear what Applicants are trying to convey. It is not clear how a polypeptide composition can be 'diagnostic' for a bacterial pathogen such as *Neisseria meningitidis* and *Neisseria gonorrhoeae*. In general, a polypeptide composition is known in the art to be 'diagnostic' of a particular disease, infection, medical condition, or clinical condition caused by a pathogen, but is not known to be 'diagnostic' for a pathogen such as a bacterial pathogen.
Clarification/correction is requested.

(b) Claims 39-46, which depend directly or indirectly from claim 25, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Remarks

29) Claims 25, 30-36, 39-42, 50, 52, 55 and 58 stand rejected. Claim 57 is allowable.

30) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

31) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hr a day and 7 days a week.

32) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

33) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Robert Mondesi, can be reached on (571) 272-0956.

/S. Devi/
Primary Examiner
AU 1645

May, 2009